IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of	:	Axel ULLRICH
Serial No.	:	09/461,090
For	:	EGF RECEPTOR TRANSACTIVATION BY G-PROTEIN COUPLED RECEPTORS REQUIRES METALLOPROTEINASE CLEAVAGE OF pro HB-EGF
Filed	:	December 14, 1999
TC/A.U.	:	1634
Examiner	:	Frank Wei Min Lu
Docket No.	:	2923-347
Customer No.	:	6449
Confirmation No.	:	3321

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

June 27, 2008

RESPONSE TO NOTICE OF NON-COMPLIANT BRIEF

Sir:

In response to the Notification of Non-Compliant Appeal Brief dated May 30, 2008, enclosed is a Supplemental Appeal Brief.

Respectfully submitted,

By

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APPELLANT'S SUPPLEMENTAL APPEAL BRIEF UNDER 37 C.F.R. §41.37

Sir:

The following comprises the Patent Owner's Brief on Appeal from the Office Action dated August 14, 2007, in which claims 40-45, 47 and 48, were finally rejected. A Notice of Appeal was filed on November 14, 2007. This Appeal Brief is accompanied by the required Appeal fee set forth in 37 C.F.R. § 41.20(b)(2), and is being timely filed on March 14, 2008.

I.

REAL PARTY IN INTEREST

The owner of the above-referenced patent and the real party in interest in this appeal is Max-Planck-Gesellschaft Zur Forderung Der Wissenschaften E.V. Munchen, Germany.

II.

RELATED APPEALS AND INTERFERENCES

The Patent Owner is unaware of any other appeals or interferences related to the subject matter of this appeal.

III.

STATUS OF CLAIMS

The rejection of claims 40-45, 47 and 48, all of the claims under consideration in the present application, is being appealed. Claims 44, 45 and 47 are independent with claims 40-43 and 48 depending directly from claim 47. No claims are allowed. The appealed claims are reproduced in the Appendix attached hereto.

Claims 1-39 and 46 were previously canceled.

IV.

STATUS OF AMENDMENTS

Claims 44, 45 and 47 were amended in the response to the non-final rejections, which was filed on June 4, 2007. No amendments were made in response to the final rejection mailed August 14, 2007. Therefore, it is believed that all amendments have been entered.

V.
SUMMARY OF THE CLAIMED SUBJECT MATTER

The present invention is directed to a method for modulating growth factor receptor activation by modulating G-protein mediated signal transduction (page 1, lines 7-9, claims 45 and 47). Prior to the present invention, growth factor receptor transactivation was generally assumed to be exclusively mediated via intracellular signals (page 10, lines 18-19). The present inventors have found that the growth factor receptor extracellular domain has a critical function in GPCR mediated transactivation. The activation of growth-factor receptors such as epidermal growth-factor receptor (EGFR) upon GPCR stimulation, requires the receptor's extracellular domain and can be mediated via an extracellular signal pathway (page 1, lines 21-23, original claims 1 and 3, claims 45 and 47). When a ligand activates heterotrimeric G-proteins by interaction with a GPCR, an intracellular signal results that induces the extracellular activity of a transmembrane metalloproteinase. This causes extracellular processing of a transmembrane growth factor precursor and release of the mature factor which directly or indirectly interacts with the exodomain of the EGFR leading to intracellular autophosphorylation and signal generation (page 17, lines 2-9). The inhibition of growth factor precursor processing has been found to block GPCR-induced growth factor receptor transactivation and downstream signals (page 1, lines 26-28). The present invention can be used for the treatment or prevention of diseases which are associated with pathological growth factor receptor transactivation. In particular, the present

invention provides a method for preventing or treating hyperproliferative diseases such as tumors, thyroid hyperplasia, retinitis pigmentosa, precocious puberty, acromegaly and asthma (page 3, lines 18-29).

In the present invention, G-protein mediated extracellular signal transduction is stimulated in a cell having a growth factor receptor tyrosine kinase which is activated by said stimulation (page 13, lines 7-10, claim 45). The growth factor receptor activation preferably occurs by tyrosine phosphorylation (page 2, lines 10-12). The G-protein mediated extracellular signal transduction pathway includes cleavage of a growth factor precursor (page 2, lines 24-31). The cell is then contacted with a compound which directly binds (page 3, line 15, claim 47) or acts (page 3, lines 8-16, claim 45) on a growth factor precursor. The growth factor receptor tyrosine kinase activation is thereby inhibited by modulating G-protein mediated signal transduction.

The present invention is also directed to a method for identifying compounds which can be used to modulate G-protein mediated signal transduction (page 6, lines 5-22, claim 44) and a method for modulating growth factor receptor activation by modulating a G-protein mediated signal transduction in a cancer cell (page 16, lines 4-19, claim 45). Modulators of G-protein mediated signal transduction are identified by contacting a cell which contains a growth factor receptor capable of being activated with a test compound suspected to be a modulator of G-protein mediated signal transduction and determining the degree of growth factor receptor activation (page 6, lines 5-14, claim 44). The cell which is contacted or stimulated can be a cell with pathologically enhanced growth factor receptor activation such as a cancer cell selected from

pancreatic, prostate, gastric, breast, thyroid, pituitary, adrenal and ovarian tumor cells (page 3, lines 23-29, claims 44 and 45)

VI.
GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The first issue on appeal is whether the invention claimed in claims 40-43, 45, 47 and 48 fails to comply with the written description requirement under 35 USC §112, first paragraph.

The second issue on appeal is whether the invention claimed in claims 44, 45 and 47 are vague and indefinite under 35 USC §112, second paragraph.

The third issue on appeal is whether the invention claimed in claims 44 and 45 can reasonably be found obvious under 35 USC §103(a) as unpatentable over Dong et al., (Proc. Natl. Acad. Sci. USA, 96, 6235-6240, May 1999) in view of Klemke, et al., (The Journal of Cell Biology, 127, 859-866, 1994).

VII.
ARGUMENTS

Claims 40-43, 45, 47 and 48 comply with the written description requirement under 35 USC §112, because they recite subject matter described in the present specification.

The Examiner contends that the language "G protein mediated extracellular signal transduction pathway which activates a growth factor receptor" is new matter.

The office action dated August 14, 2007,states that ""[A]lthough original claim 1 contains the language "G protein mediated signal transduction" and original claim 3 contains "an extracellular signal pathway", and page 2 lines 7-10 of the specification describes that activation of the growth-factor receptor is mediated by its extracellular domain and via an extracellular signal pathway, these descriptions only supports that growth-factor receptor is mediated by its extracellular domain in G protein mediated signal transduction"". Applicants respectfully contend that the originally filed application supports the language "G protein mediated extracellular signal transduction pathway which activates a growth factor receptor". Page 2, lines 5-22 clearly describe a G-protein mediated signal transduction pathway which leads to the activation of a growth factor receptor via its extracellular domain and an extracellular signal pathway. Original claim 3 depends from claim 1 and recites that the activation of the growth factor receptor is mediated via an extracellular signal pathway. Original claim 1 indicates that the growth factor receptor is capable of being modulated with a modulator of G-protein mediated signal transduction.

In addition, it is shown on page 10, lines 25-32 that the GPCR ligand bound activation of the growth factor receptor does not comprise the intracellular domain. For this reason, a chimeric receptor, which contains the extracellular domain of EGFR and the intracellular domain of the PDGFR, has been activated in RAT1 cells by adding GPCR ligands. A complete PDGF receptor (extra-/intracellular domain) is in this cell type, however, it is not activated by adding GPCR ligands. Obviously, the intracellular domain of the PDGF receptor is not sufficient for the GPCR ligand bound one according to the

invention. One skilled in the art would conclude that the activation has to take place extracellularly, otherwise both receptor types, i.e. chimeric and complete receptor, would be activated by the addition of GPCR ligands (see also Figure Ib and Id and page 11, lines 2-16).

This correlation is confirmed in the present invention by the Examples described on page 11, lines 26-32 and page 12, lines 1-13. It is disclosed therein that the activation of a GPCR bound signal pathway in a cell induces the activation of a growth factor receptor at a second cell, which is in the immediate proximity (Figure 2a). Thus, there is an intercellular and also an extracellular signal pathway from one cell to the other. Applicants previously pointed out that the exact language used in the claims does not need to appear in the specification. MPEP §2163.02 states that the "subject matter of the claim need not be described literally (i.e. using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement". MPEP §2163.07(a) indicates that if a disclosed device inherently performs a function or has a property, the patent application discloses that function or property even if it says nothing explicit concerning it and the application may later be amended to recite the function without introducing new matter. The Board of Patent Appeals and Interferences also interpreted the written description requirement in Ex parte Holt, 19 USPQ2d 1211 (Bd Pat App & Inter, 1991) and in Ex parte Eggleston, et al, Appeal No. 2003-2074. In Holt the claims were directed to a component having a channel. The Examiner rejected the claims as lacking adequate support for the channel. The Board held that the figures illustrate a channel in accordance with the common and accepted meaning of the term.

The Board stated that "It is well established that the invention claimed need not be described ipsis verbis in the specification in order to satisfy the disclosure requirements of 35 U.S.C. §112". In Eggleston, the claims were directed to a method of forwarding messages between a host system and a mobile client. The Examiner contended that an explicit limitation in the claims was not present in the written description. The Board stated that explicit disclosure of the claimed term is not required under 35 U.S.C. §112, first paragraph. Applicants respectfully contend that the language "G protein mediated extracellular signal transduction pathway which activates a growth factor receptor" is not new matter.

The office action dated August 14, 2007 also indicates that "CRM197, a catalytically inactive form of the diphtheria toxin, which specifically binds to proHB-EGF and which is capable of blocking the processing of proHB-EGF by metalloproteinase" cannot serve as a compound which directly acts on a growth factor precursor in a G protein mediated extracellular signal transduction pathway which activates a growth factor receptor. Page 3, of the office action states that it is known that EGF is released from its precursor by metalloproteinase and EGFR is activated by EGF and thus ""CRM197 cannot serves "a compound which directly acts on a growth factor precursor in a G protein mediated extracellular signal transduction pathway which activates a growth factor receptor" as recited in claims 45 and 47"". Applicants respectfully point out that CRM197 directly binds to a growth factor precursor, namely Pro HB-EGF, which is part of a G protein mediated extracellular signal transduction pathway. The binding of CRM197 blocks the processing of the precursor by a metalloproteinase thereby

interrupting the pathway and inhibiting the release of soluble growth factor which prevents the activation of a growth factor receptor. In view of this, applicants contend that CRM197 is a compound which directly acts on a growth factor precursor in a G protein mediated extracellular signal transduction pathway which activates a growth factor receptor and thus the claims are supported by the disclosure in the originally filed application.

The Examiner contends that the language "wherein said cancer cell is selected from the group consisting of pancreatic, prostate, gastric, breast, thyroid, pituitary, adrenal and ovarian tumor cells" in claims 44 and 45 is new matter with regard to *in vitro* methods. Applicants point out the disclosure on page 3, lines 23-27 of the present application which states that "the present invention provides methods for preventing or treating, among other diseases, hyperproliferative diseases such as colon, pancreatic, prostate, gastric, breast, lung, thyroid, pituitary, adrenal and ovarian tumors, as well as thyroid hyperplasia, retinitis pigmentosa, precocious puberty, acromegaly and asthma". In addition, pages 16 and 17 in the present application discuss human prostate cancer cells and page 6, lines 5-14 discuss the claimed method for identifying modulators of G-protein mediated signal transduction using a cell which contains a growth factor receptor. Since page 3 of the present application indicates that the present invention can be used to treat pancreatic, prostate, gastric, breast, thyroid, pituitary, adrenal and ovarian tumors, one skilled in the art would know that cells from these tumors have a growth factor receptor tyrosine kinase and thus one would reasonably expect such cells to be useful to identify test compounds as in claim 44. Regarding claim 45, applicants

point out that treating the tumors discussed on page 3 of the present application using the present invention inherently results in the treatment of a cancer cell as in claim 45. In addition, page 4, lines 2-4 indicate that the contacting step may occur in vitro, e.g. in a cell culture or *in vivo*, e.g. in a subject in need of medical treatment. Therefore, the present inventors were in possession of and disclosed the subject matter claimed in claims 44 and 45. In view of the above discussion, applicants contend that the present claims do not include new matter and request that this rejection be withdrawn.

Claims 40-45, 47 and 48 are not vague and indefinite under 35 USC §112, second paragraph.

Claim 44 was rejected as vague and indefinite as to how one would know in which situation the test compound can be considered as a compound that has the ability to modulate a G-protein mediated signal transduction. Claim 44 includes the step of "evaluating G-protein mediated receptor tyrosine kinase activation upon exposure of the cancer cell to said test compound as an indication of said test compound's ability to modulate G-protein mediated signal transduction thereby identifying a test compound for modulating G-protein mediated signal transduction". One skilled in the art would know that if G-protein mediated receptor tyrosine kinase activation does not occur upon the exposure of the cancer cell to a test compound, then the test compound has modulated the G-protein mediated signal transduction. Claim 44 recites that the test compound is suspected to act on a precursor of a ligand of the receptor tyrosine kinase. If

the test compound binds or acts on a precursor of a ligand of the receptor tyrosine kinase the G-protein mediated signal transduction pathway will be interrupted and there will not be G-protein mediated receptor tyrosine kinase activation. Applicants contend that one skilled in the art would know that if the test compound binds or acts on a precursor of a ligand of the receptor tyrosine kinase, there will be no G-protein mediated receptor tyrosine kinase activation. In view of the above discussion, applicants contend that claim 44 is not vague or indefinite.

Claims 45 and 47 were rejected as vague and indefinite regarding how to modulate the receptor tyrosine kinase activation by G-protein mediated signal transduction. Claims 45 and 47 both recite stimulating G-protein mediated signal transduction in a cell having a growth factor receptor tyrosine kinase and then contacting the cell with a compound which directly binds to or acts on a growth factor precursor in a G protein mediated extracellular signal transduction pathway which activates a growth factor receptor. The compound binds to or acts on the growth factor precursor, interrupting the signal transduction pathway and thereby modulating the growth factor receptor tyrosine kinase activation by G-protein-mediated signal transduction. Since both claim 45 and claim 47 recite that the cell is contacted with a compound which directly binds to or acts on a growth factor precursor in a G protein mediated extracellular signal transduction pathway which activates a growth factor receptor, applicants contend that one skilled in

the art would know how the receptor tyrosine kinase activation is modulated by G-protein mediated signal transduction.

Claims 44 and 45 are not obvious over Dong et al., Proc. Natl. Acad. Sci. USA, 96, 6235-6240 (May 1999) in view of Klemke et al., The Journal of Cell Biology, 127, 859-866 (1994) because claims 44 and 45 recite subject matter not shown or suggested by the cited prior art.

Klemke et al. was cited for the disclosure of a human pancreatic carcinoma cell containing EGFR. Klemke does not suggest or disclose a method for modulating G-protein modulated signal transduction. Dong et al. does not reference the G protein and discusses only the inhibition of autocrine signal transduction by means of EGFR. Dong teaches the incubation of HMEC cells with batimastat or mAb225 and then treating the cells with EGF. Applicants note that on page 4 of the advisory action dated September 23, 2003, the examiner agrees that "one skilled in the art would not have expected batimastat, which acts on an extracellular pathway of EGFR, to be capable of modulating a G protein mediated signal transduction". Applicants respectfully point out that at the time of the present invention, it was believed that the correlation between G protein activation and the activation of tyrosine phosphorylation of EGFR was mediated by an intracellular pathway. Thus, one skilled in the art would not have expected batimastat, which acts on an extracellular pathway of EGFR, to be capable of modulating a G protein mediated signal transduction. As indicated on page 6 of the office action dated May 20, 2003, Dong does not directly show that their method is related to modulation of G-protein mediated signal transduction. Applicants contend that in view of the knowledge in the art, one skilled in the art would not have been motivated to modify Dong's method to modulate G protein mediated signal transduction.

In contrast to the advisory action dated September 23, 2003, the office action dated May 20, 2003 states: "*since it is known that reduction of tyrosine phosphorylation of a receptor is correlated to activation of G protein, batimastat used in the method of Dong et al. also modulate G protein mediated signal transduction.*" Applicants point out that this statement is both incomplete and incorrect. A correlation of G protein activation and the activation of tyrosine phosphorylation of EGFR was indeed known in the art. It was assumed, however, that this correlation is mediated by an intracellular pathway. Thus, prior to the present invention, one skilled in the art could not reasonably have expected that batimastat as used in the method of Dong et al. (which acts on a different extracellular activation pathway of EGFR mediated by addition of EGF) would be capable of modulating a G protein mediated signal transduction. The activation of receptor tyrosine kinases such EGFR can be effected via a plurality of different pathways. As explained in detail below, a number of different stimuli were known, in addition to the activation of G proteins, which were correlated with EGFR tyrosine phosphorylation at the time of the Dong et al publication. For example, it had been reported at the time of Dong et al. that the stimulation of cytokine receptors leads to tyrosine phosphorylation of the EGF receptor (Yamaguchi et al., 1997, Tyrosine phosphorylation of the EGF receptor by the kinase JAK2 is induced by growth hormone. Nature 390: 91-96). However, in contrast to the mechanism observed by Dong et al., this pathway involves the JAK family of intracellular non-receptor tyrosine kinases and requires the intracellular adaptor-docking function of the EGF receptor (Yamaguchi et al., 1997).

It was also known at the time of Dong et al. that members of the integrin family of cell surface receptors can modulate EGFR tyrosine phosphorylation in order to generate further cellular responses (Moro et al., 1998, Integrins induced activation of the EGF receptor: role in MAP kinase induced and adhesion-dependent cell survival. EMBO J 17: 6622-6632). However, again in contrast to the mechanism observed by Dong et al., this pathway is independent of EGFR ligands and involves cell adhesion dependent interaction of integrins with the EGFR (Moro et al., 1998).

Furthermore, it was well documented at the time of Dong et al. that a number of exogenous stress stimuli, both physical and chemical, initiate signal transduction pathways in cells that are part of stress responses. In particular, UV radiation had been reported to promote enhanced tyrosine phosphorylation of the EGF receptor (Warmuth et al., 1994. Ultraviolet radiation induces phosphorylation of the epidermal growth factor receptor. Cancer Res. 54: 374-376). However, as UV activates v-erbB, an oncogenic isoform of the chicken EGF-receptor that lacks a ligand-binding domain, the mechanism of UV-induced EGFR activation occurs ligand-independently (Knebel et al 1996, Dephosphorylation of receptor tyrosine kinases as target of regulation by radiation, oxidants or alkylating agents. EMBO J. 15: 5314-5325). In fact, activation of the EGFR is indirect through inactivation of phosphotyrosine phosphatases (Knebel et al., 1996). Finally, it had been demonstrated at the time of Dong et al. that the phorbol ester TPA (12-O-tetradecanoylphorbol-13-acetate) promotes EGFR tyrosine phosphorylation via its intracellular receptor protein kinase C (Xian, W. et a., 1995, Activation of the epidermal growth factor receptor by skin tumor promoters and in skin tumor from

SENCAR mice, Cell Growth & Differentiation 6: 1447-1455; Emkey and Kahn, 1997, Cross-talk between phorbol ester-mediated signaling and tyrosine proto-oncogenes, J. Bio. Chem. 272: 31172-31181). The present application (see also Prenzel et al., 1999) discloses that this TPA-induced transactivation of the EGF receptor occurs via metalloproteases and HB-EGF but is clearly distinct from GPCR mediated EGFR receptor activation since the receptor activation is not by GPCR (see Figures 2c and 3a of the present application).

Applicants contend that one skilled in the art would not assume from the mere correlation of the effect of the compound according to Dong et al. on the proteolytic release of EGFR ligands that it modulates GPCR mediated EGFR tyrosine phosphorylation, particularly since there were non-GPCR mediated EGFR tyrosine phosphorylation pathways which are also inhibited by batimastat. At the time of Dong et al. it was commonly believed that GPCR stimulation of EGFR activation itself did not involve proteolytic cleavage of ligand precursors. For example, at the time of Dong et al. it was generally acknowledged that the mechanism by which GPCRs modulate tyrosine phosphorylation of the EGF receptor is centered on the mediation by the non-receptor tyrosine kinase c-Src, which was reported to be coupled to nearly all GPCRs that lead to EGF receptor phosphorylation (reviewed in Thomas and Brugge, 1997, Cellular functions regulated by Src family kinases. Annu. Cell Dev. Biol. 13: 513-609). Over expression of either a dominant-negative Src construct or Csk, a regulatory kinase that inhibits Src function, decreases EGF receptor tyrosine phosphorylation provoked by activation of LPA or α2 adrenergic receptors (Luttrell et al., 1997, Gby subunits

mediated Src-dependent phosphorylation of the epidermal growth factor receptor. A scaffold for G protein-coupled receptor mediated Ras activation. J. Biol. Chem. 272:4637-4644). The mediator role of Src was suggested to be direct in that Src is able to associate with and phosphorylate the EGF receptor *in vivo* and *in vitro* (Thomas and Brugge, 1997). This mechanism would predict the existence of Src-EGF receptor complexes provoked by activation of GPCR. The evidence for this was shown by the demonstrations that angiotensin II (Eguchi et al., 1998, Calcium-dependent epidermal growth factor receptor transactivation mediates the angiotensin II-induced mitogen-activated protein kinase activation in vascular 2smooth muscle cells, J. Biol. Chem. 273: 8890-8896) or LPA (Luttrell et al., 1997) rapidly increases the amount of Src coprecipitated with EGF receptors.

Furthermore, calcium influx was reported to be sufficient to trigger EGFR tyrosine kinase phosphorylation and MAP kinase activation in PC12 cells (Rosen and Greenberg, 1996, Stimulation of growth factor receptor signal transduction by activation of voltage-sensitive calcium channels. Proc. Natl. Acd. Sci. USA 93: 1113-1118). This had been extended subsequently since several findings had demonstrated Ca^{2+} to be necessary for EGFR-transactivation induced by GPCR-ligands (Eguchi et al., 1998; Eguchi et al., 1999, Involvement of PYK2 in angiotensin II signaling of vascular smooth muscle cells, Hypertension 33: 201-206; Soltoff 1998, Related adhesion focal tyrosine kinase and the epidermal growth factor receptor mediate the stimulation of mitogen-activated protein kinase by the G-protein-coupled P-2Y2 receptor, J. Biol. Chem 273: 23110-23117). Due to this critical function of Ca^{2+}, Ca-regulated FAK family kinase

PYK2 was discussed as a mediator of EGFR transactivation in the signaling elicited by GPCR ligands upstream of the EGFR signal (Eguchi, 1999; Soltoff 1998).

As discussed above, the correlation of GPCR-induction of EGFR activation via a pathway comprising extracellular elements is not suggested or disclosed by Dong et al. Thus one skilled in the art would not be motivated to modify Dong et al to contact a cancer cell with a compound which affects an extracellular signal pathway as required by claims 44 and 45.

Enclosed is a diagram which shows the signal transduction pathway starting from a dysfunction of G-protein signal transduction and resulting in a receptor tyrosine kinase activation. In the presently claimed method, the modulator acts on a precursor of a ligand of the receptor tyrosine kinase or on a growth factor precursor in a G-protein mediated extracellular signal pathway which activates a growth factor receptor. In contrast to claims 44 and 45, Dong uses batimastat which inhibits the metallo-proteinase. Thus, the present invention inhibits receptor tyrosine kinase transactivation by a different mechanism. For example, the recognition sequence for a metalloproteinase may be masked by binding of the modulator in the present method or the binding of the modulator may inhibit the binding of the growth factor to the receptor. Though Dong's method can interrupt the whole signal cascade, the present invention interrupts the signal cascade in a different way. In the present invention a compound acts on the growth factor precursor inhibiting processing of the precursor and interrupting the signal cascade. Thus, the present inventors have shown for the first time that modulators which act on a growth factor precursor to inhibit the activation of

the extracellular domain of a growth factor receptor are suitable for the treatment of disorders, in particular of cancers, which are induced by G- protein mediated signal transduction. In contrast to the present invention, Dong discloses only that the inhibitory effect of batimastat on metastasis is due to interference with autocrine EGFR signaling. Thus, Dong does not suggest or disclose a method for identifying and providing modulators according to the present invention as Dong suggests only Batimastat, which is a compound which acts on a metalloproteinase. In addition, applicants respectfully point out that the addition of EGF as disclosed in Dong, does not activate the G-protein or GPCR initiated extracellular signal transduction pathway. The addition of EGF causes a stimulation of EGFR which is different from the stimulation which proceeds via the G-protein or GPCR initiated extracellular signal transduction pathway as required in the present claims. Figure 4 in the present application shows the influence of the addition of various reagents such as TPA, bombesin, carbachol and EGF, on the stimulation of the GPCR-initiated signal transduction pathway. This stimulation is shown by the detection of processed HB-EGF-1 (Fig 4A). Though the detection of processed HB-EGF-1 is possible after the addition of TPA, bombesin, and carbachol, no HB-EGF-1 is detectable after preincubation with EGF (Fig. 4A, right column). Figure 4a in the present application clearly shows that EGF, in contrast to TPA, bombesin and carbachol, is not an activator of the GPCR initiated signal transduction pathway. In view of this, applicants contend that Dong does not suggest stimulating G-protein mediated signal transduction in a cancer cell or contacting the cell with a compound which acts on a growth factor precursor as required in claims 44 and 45.

In summary, Dong and Klemke individually and in combination do not reference the G protein and Dong only discusses the inhibition of autocrine signal transduction by means of EGFR, Dong uses batimastat which inhibits the metallo-proteinase and at the time of the present invention, it was believed that the correlation between G protein activation and the activation of tyrosine phosphorylation of EGFR was mediated by an intracellular pathway while batimastat acts on an extracellular pathway of EGFR. Therefore, one skilled in the art would not have modified Dong's method in view of Klemke and in order to modulate a G protein mediated signal transduction in a cancer cell. Therefore, the applicant submits that the outstanding rejection of claims 44 and 45 is improper and should be withdrawn.

Conclusion

For all of the above noted reasons, it is strongly contended that claims 40-43, 45, 47 and 48 comply with the written description requirement under 35 USC §112, claims 40-45, 47 and 48 are not vague and indefinite under 35 USC §112, second paragraph and that certain clear differences exist between the present invention as claimed in claims 44 and 45 and the prior art relied upon by the Examiner. It is further contended that these differences are more than sufficient evidence that the present invention would not have been obvious to a person having ordinary skill in the art at the time the invention was made.

This final rejection being in error, therefore, it is respectfully requested that this honorable Board of Patent Appeals and Interferences reverse the Examiner's decision in this case and indicate the allowability of claims 40-45, 47 and 48.

In the event that this paper is not being timely filed, the Patent Owner respectfully petitions for an appropriate extension of time. Please charge any fee or credit any overpayment pursuant to 37 §C.F.R. 1.16 or §1.17 to Deposit Account No. 02-2135.

Respectfully submitted,

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VIII.

APPENDIX OF CLAIMS ON APPEAL

Claims 1-39 (Cancelled)

40. The method according to claim 47, wherein said receptor tyrosine kinase is epidermal growth factor receptor (EGFR).

41. The method according to claim 47, wherein said growth factor precursor is proheparin-epidermal growth factor (proHB-EGF) and said receptor tyrosine kinase is EGFR.

42. The method according to claim 47, wherein said receptor tyrosine kinase is selected from the group consisting of epidermal growth factor receptor (EGFR), human epidermal growth factor receptor-2 (HER-2), human epidermal growth factor receptor-3 (HER-3), human epidermal growth factor receptor-4 (HER-4), Tumor Necrosis Factor receptor 1 (TNF receptor 1), Tumor Necrosis Factor receptor 2 (TNF receptor 2), tumor necrosis factor receptor superfamily, member 8 (CD 30) and interleukin 6 receptor (IL-6 receptor).

43. The method according to claim 47, wherein said receptor tyrosine kinase is selected from the group consisting of EGFR and other members of the EGFR family.

44. A method for identifying a test compound for modulating G-protein mediated signal transduction, comprising contacting a cancer cell containing a receptor tyrosine kinase capable of activation by G-protein mediated signal transduction with a test compound suspected to act on a precursor of a ligand of the receptor tyrosine kinase, and evaluating G-protein mediated receptor tyrosine kinase activation upon exposure of the cancer cell to said test compound as an indication of said test compound's ability to modulate G-protein mediated signal transduction thereby identifying a test compound for modulating G-protein mediated signal transduction, wherein said cancer cell is selected from the group consisting of pancreatic, prostate, gastric, breast, thyroid, pituitary, adrenal and ovarian tumor cells.

45. A method for modulating growth factor receptor activation by modulating a G-protein mediated signal transduction, comprising:

stimulating G protein mediated signal transduction in a cancer cell having a growth factor receptor tyrosine kinase, wherein the growth factor receptor tyrosine kinase is activated, and wherein said growth factor receptor tyrosine kinase is selected from the group consisting of EGFR and other members of the EGFR family, said cancer cell comprising an extracellular EGFR domain and having a G-protein mediated signal transduction pathway which activates a growth factor receptor, wherein one or more tyrosine residues are phosphorylated based on the activation of said G-protein mediated signal transduction pathway, the extracellular domain of said receptor is

capable of binding to its receptor ligand, and said ligand is generated from a precursor of said ligand by a proteinase-dependent cleavage; and

contacting said cancer cell with a compound which acts on a growth factor precursor in a G protein mediated extracellular signal pathway which activates a growth factor receptor, and thereby modulating the growth factor receptor tyrosine kinase activation by G-protein mediated signal transduction, wherein said cancer cell is selected from the group consisting of pancreatic, prostate, gastric, breast, thyroid, pituitary, adrenal and ovarian tumor cells.

46. (Canceled)

47. A method for modulating growth factor receptor activation by modulating G-protein mediated signal transduction comprising:

stimulating G protein mediated signal transduction in a cell having a growth factor receptor tyrosine kinase, wherein the growth factor receptor tyrosine kinase is activated; and

contacting the cell with a compound which directly binds to a growth factor precursor in a G protein mediated extracellular signal transduction pathway which activates a growth factor receptor, wherein said G protein mediated extracellular signal transduction pathway includes cleavage of a growth factor precursor, thereby modulating the growth factor receptor tyrosine kinase activation by G-protein-mediated signal transduction.

48. The method according to claim 47, wherein said cell is an ovarian cancer cell or a prostate cancer cell.

IX.

Evidence Appendix

A copy of the background references discussed above and in the applicant's prior responses are included with this brief. These references were discussed in applicant's August 20, 2003 response. Also included is a chart showing the G-protein signal transduction pathway which was submitted with applicant's November 28, 2005 response.

X.

RELATED PROCEEDINGS APPENDIX

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